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Jayoti Vidyapeeth Women's University, Jaipur

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A Study on the Biological Evaluation of Novel Benzothiazole Derivatives including Anti-microbial and Anti-diabetic Activity

A Synopsis

Submitted in

Partial fulfillment for the degree of

Doctor of Philosophy

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Submitted to :

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DECLARATION

I. I, **Manisha Kumari Sharma** hereby declare that all the statement made in this application are true, complete and correct to the best of my knowledge and belief and in the event of any information being found false or incorrect or any ineligibility being detected before or after the registration for Ph.D. My candidature is liable to be cancelled and legal action may be initiated against me.

II. I have deposited the required fee, as notified by the University regularly.

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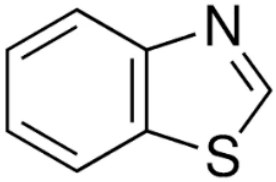
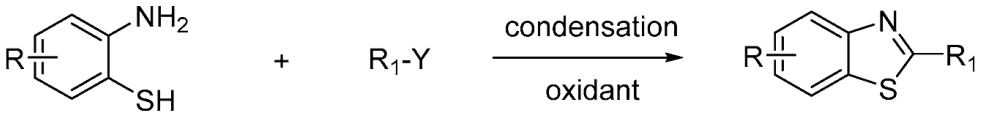
Introduction: -

Interest and research centred on the development of innovative pharmaceutical drugs is always increasing. Heterocycles, a category of chemical compounds including at least one non-carbon atom in their ring structure, have been acknowledged as essential frameworks in medicinal chemistry due to their importance in drug discovery and development. Their structural variety and adaptability render them appealing building blocks used in drug design for antibiotics, antivirals, antifungals, anticancer agents, antioxidants and neuroprotective compounds, facilitating new therapy and enhanced patient outcomes. Recent improvements in synthetic techniques and computational tools have facilitated straightforward synthetic accessibility, enabling the rational design and optimization of heterocyclic compounds with improved biological activities via a more profound comprehension of structure–activity correlations. This has resulted in the emergence of intriguing novel pharmaceutical candidates with enhanced therapeutic characteristics (Pibiri 2024). Benzothiazole belongs to a family of sulfur-containing heterocyclic compounds consisting of a benzene ring fused with a thiazole ring.



Benzothiazole is prevalent in several natural compounds due to its significant applicability in phytohormones, antioxidants, electroluminescent devices, vulcanization inducers, and enzyme inhibitors. Benzothiazole is significant in medicinal chemistry, offering a diverse array of molecules with applications in antibacterial, antiviral, antimicrobial, anticancer, antioxidant, anti-inflammatory, antituberculosis, antiparkinsonian, muscle relaxant and enzyme inhibitory activities. A range of synthetic methods has been developed for the synthesis of

benzothiazole derivatives(Sharma et al. 2021).A. W. Hofmann first synthesized 2-substituted BTA in 1887 because of its varied action and simple cyclization method(Patil et al. 2014).Since then, a multitude of synthetic pathways have been executed and documented. Jacobson's cyclization of thiobenzanilides is a prevalent technique for synthesizing BTA(Sadek et al. 2012).Moreover, the synthesis of benzothiazole derivatives has been accomplished by several synthetic routes. The predominant technique for manufacturing benzothiazole compounds involves the condensation of 2-aminobenzenethiol with cyano or carbonyl groups(Gao et al. 2020).



Y= CHO, COX, COOH, COOR, CN, etc.

Several studies have identified that aniline may be used to synthesize benzothiazoles by its reaction with substances such as carbon disulfide, piperidine and isothiocyanate. Nonetheless, these traditional methods are associated with many disadvantages, like limited yield, poor selectivity, harsh reaction conditions or use of hazardous chemicals.Benzothiazole is a compound belonging to a broad category of heterocycles which include sulfur and consist of a fused benzene and thiazole ring. Benzothiazole is a vital element in medicinal chemistry, yielding several compounds with antibacterial, antiviral, antimicrobial and anticancer properties. The synthesis and derivatization of benzothiazole moieties are crucial owing to their widespread uses in industry and medicine(Pal et al. 2024).Benzothiazole (BTA) and its derivatives are significant heterocyclic chemicals, prevalent in natural products and medicinal agents. It exhibits several pharmacological characteristics and many of its analogues display structural variety, facilitating the development of novel therapeutic medications. BTA derivatives have a wide range of pharmacological

effects. The advancement of medicinal chemistry including BTA has been swift and vigorous (Ameer et al. 2022).Therefore, in view of this, this study focuses on synthesizing benzothiazole derivatives which are biologically active, specifically exhibiting anti-microbial and anti-diabetic activity.

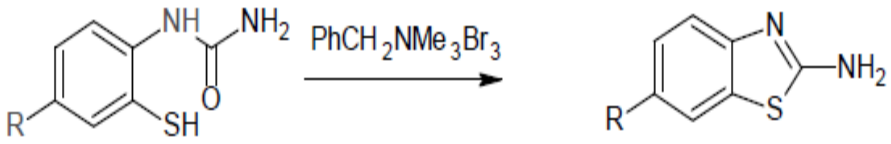
Review of Literature: -

This review seeks to consolidate and critically evaluate the existing research on the synthesis of biologically active benzothiazole derivatives. This review focuses on recent research findings, emphasizing progress in the synthesis, characterisation and evaluation of the bioactivity of benzothiazole derivatives.

1. Synthetic strategies/pathways of benzothiazole compounds:

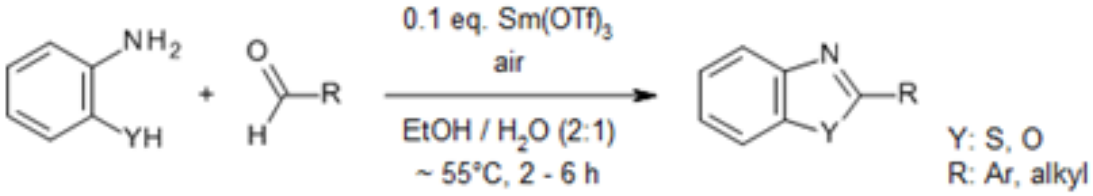
Synthesis of 2-aminobenzothiazoles using a C-S bond formation strategy was reported by **Batey and Evindar (2003)**. With the aid of copper and palladium-catalyst, a C-S link was established within the molecule. For the production of 2-amino benzothiazoles, it was shown that copper and palladium can catalyse the creation of intramolecular C-S bonds via cross coupling between aryl halide and thioureas functionalities.

For synthesis of 2-aminobenzothiazoles, **Jordan and Reitz (2003)** employed benzyltrimethylammonium tribromide ($PhCH_2NMe_3Br_3$), an electrophilic bromine source.

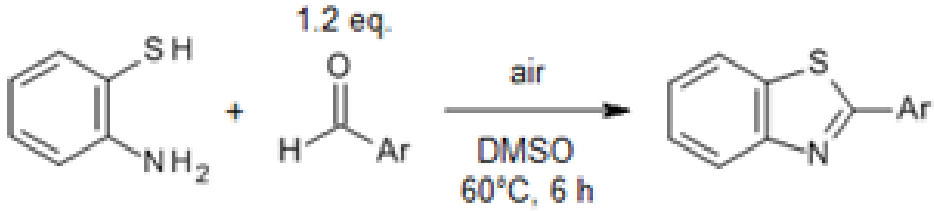


Patel and colleagues (2006) were able to synthesise a wide range of 2(5or6)-substituted aminobenzothiazoles.

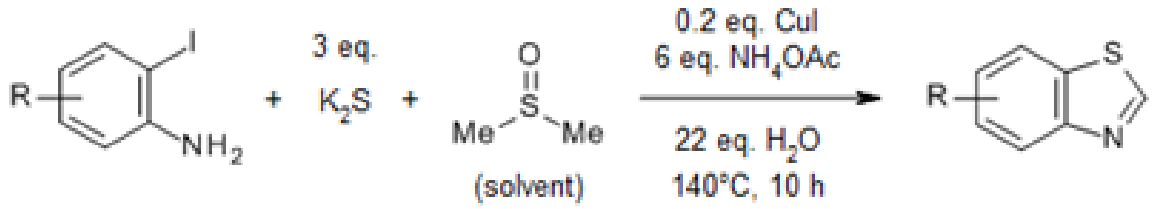
Mane et al. (2013) facilitated a simple, eco-friendly and effective approach the synthesis of benzoxazoles and benzothiazoles from o-amino (thio) phenols and aldehydes, using samarium triflate as a recyclable acid catalyst under moderate reaction conditions in an aqueous medium.



Miao et al. (2016) proposed a facile synthesis of 2-arylbenzothiazoles from 2-aminothiophenol and aryl aldehydes using an air/DMSO oxidant system, characterized by operational simplicity, catalyst-free conditions, compatibility with diverse functionalities, and yielding products in good to excellent yields.

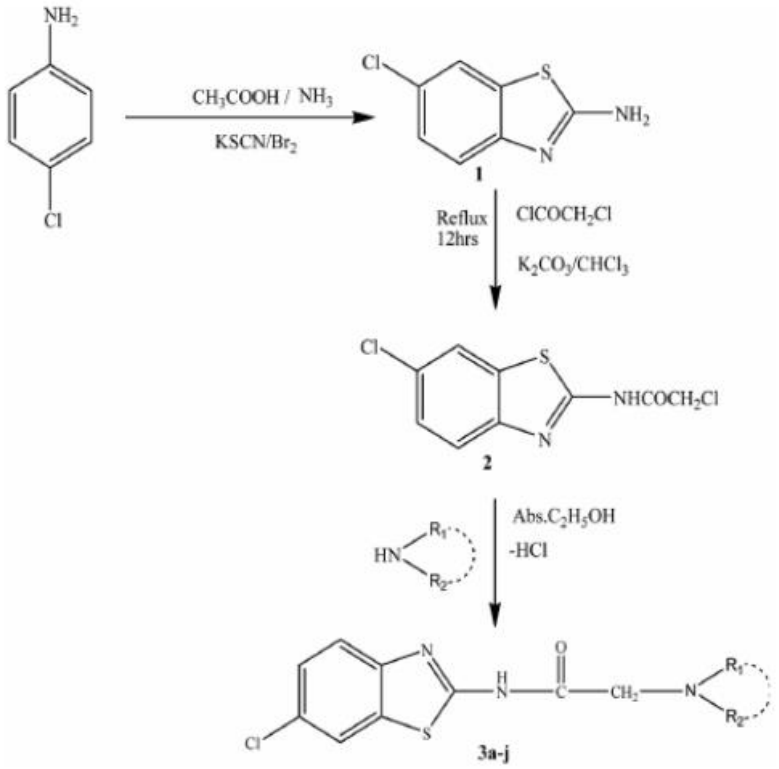


Zhang et al. (2020) described a three-component reaction involving o-iodoanilines or electron-rich aromatic amines with K_2S and DMSO. A comparable reaction of o-phenylenediamines yielded 2-unsubstituted benzimidazoles in the absence of K_2S. DMSO serves three essential functions: as a carbon source, solvent, and oxidant.



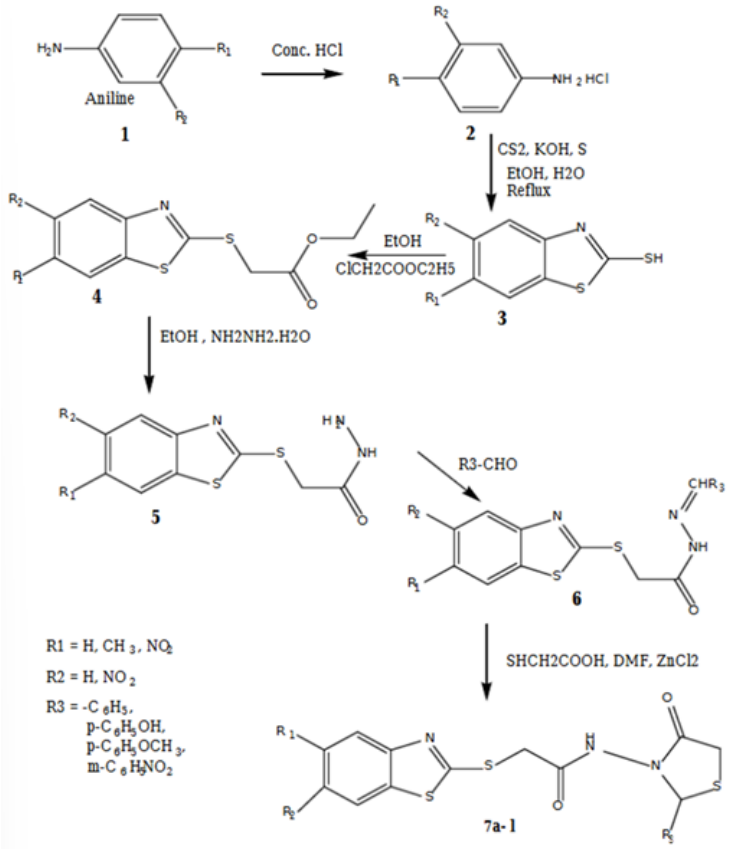
2. Anti-diabetic activity of benzothiazole compounds:

Mariappan et al. (2012) synthesized a new series of benzothiazole compounds and evaluated their hypoglycemic efficacy in vivo using a streptozotocin-induced diabetic rat model. These compounds demonstrated significant biological activity in comparison to glibenclamide, a strong and well-established antidiabetic medication used as a reference medicine. All drugs demonstrated efficacyat a dosage of 100 mg/kg orally. The experimental findings were statistically significant at the $p<0.01$ and $p<0.05$ levels.

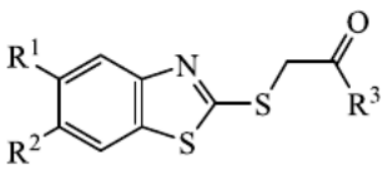


Rathore et al. (2017) synthesized a new class of benzothiazole derivatives. Compounds 7(a-l) and synthesized derivatives were characterized for various physical and chemical parameters. All synthesized compounds exhibited

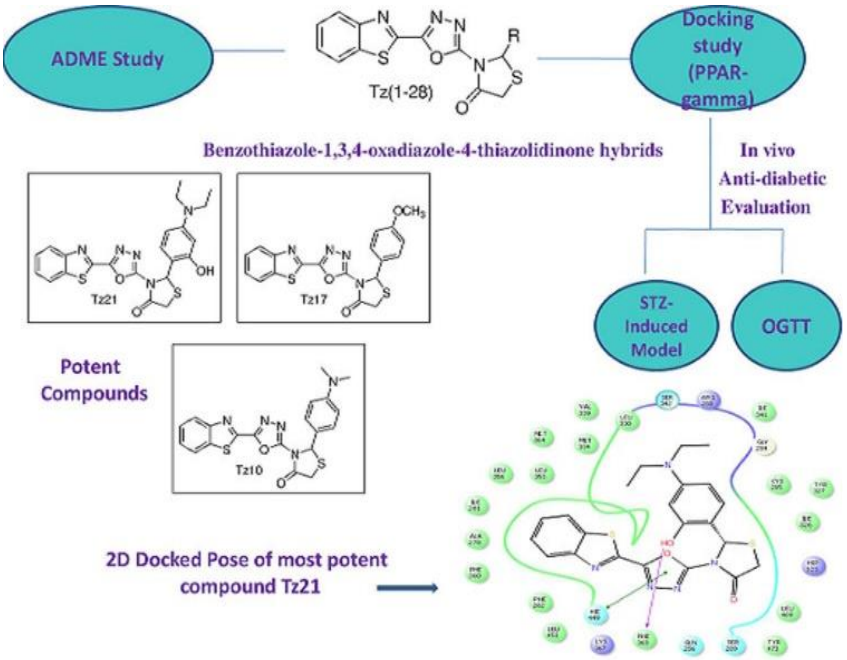
substantial biological effectiveness. All compounds demonstrated efficacy, with experimental findings achieving statistical significance at $p<0.05$ levels. The findings indicate that compounds exhibited significant anti-diabetic action and may be advantageous for future medication development targeting metabolic disorders.



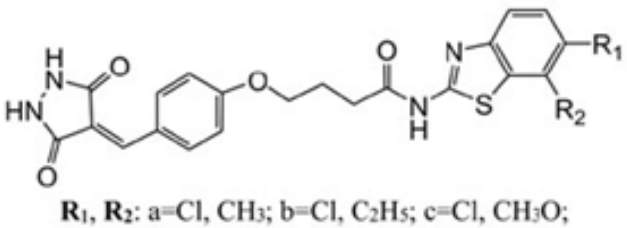
Mirza et al. (2019) assessed derivatives of 2-mercapto benzothiazoles for their in vitro α-glucosidase inhibitory efficacy. Compounds exhibited very powerful α-glucosidase inhibitory action, with IC50 values ranging from 31.21 to 208.63 μM, in contrast to the conventional medication acarbose, which had an IC50 of 875.75 ± 2.08 μM. Several substances were found as having dual functionality as antiglycating agents and α-glucosidase inhibitors.



Butani et al. (2019) produced a series of novel benzothiazole-1,3,4-oxadiazole-4-thiazolidinone hybrid analogs (Tz1-Tz28) to identify potential anti-diabetic medicines. The prediction of drug-like qualities using Molinspiration online program indicated that all produced compounds possessed the potential to become orally active molecules.



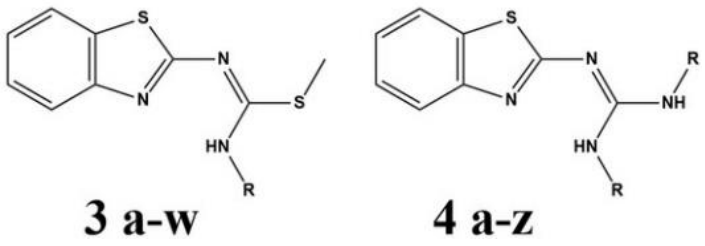
Haroun (2019) developed a variety of benzothiazole-pyrazolidinedione hybrids and assessed their antidiabetic efficacy, accompanied by molecular docking and in silico analysis. Remarkably, 5a, 5b, and 5c exhibited more potency than the normal medication. The newly synthesized hybrids represented a novel category of antidiabetic medicines.



R_1, R_2: a=Cl, CH_3; b=Cl, C_2H_5; c=Cl, CH_3O;
d= CH_3O, CH_3; e=CH_3O, C_2H_5; f= CH_3O, CH_3O

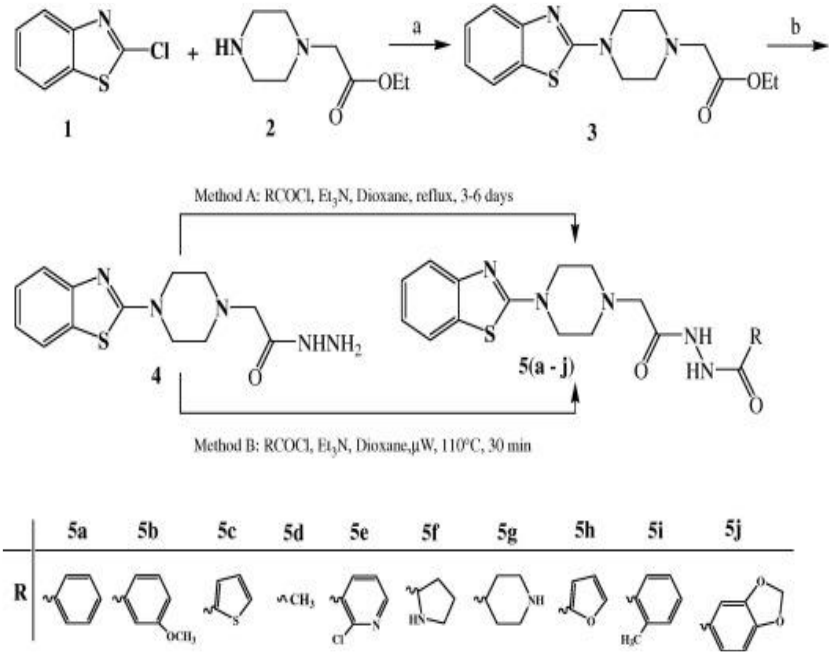
Salazar et al. (2025) sought to assess in silico and in vivo, two series of 2-aminobenzothiazole derivatives. Compounds effectively lowered blood glucose

levels (<200 mg/dL) and improved the lipid profile. Consequently, they may serve as potential antidiabetic medicines in the future.



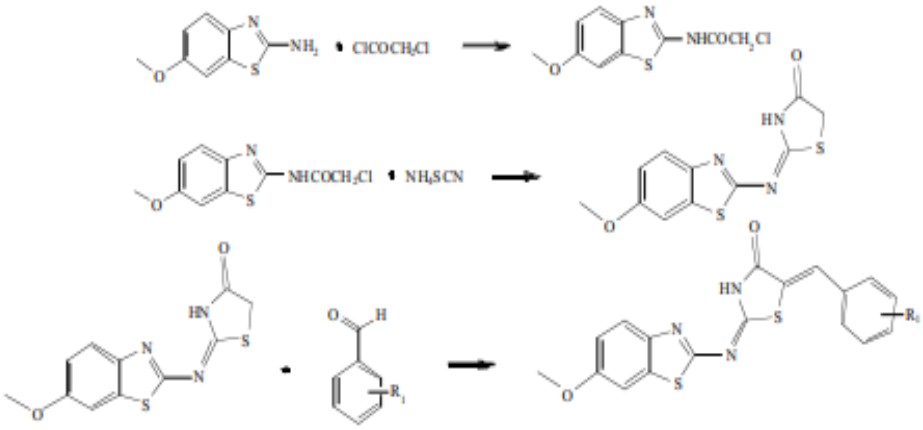
3. Anti-microbial activity of benzothiazole compounds:

Sharma et al. (2010) synthesized benzothiazole derivatives. The structures of the synthesized compounds were analyzed using spectrum data and elemental analysis. An antibacterial activity assay was conducted on all synthesized compounds, yielding findings of enhanced efficacy.



Benzothiazole molecules were synthesized by **Haroun et al. (2018)** via conventional organic synthesis methods. Microdilution was used to evaluate antibacterial efficacy. Twelve synthesized compounds exhibited antibacterial properties. Regarding antifungal efficacy, the compounds surpassed the reference drugs bifonazole and ketoconazole in most cases. The cytotoxicity prediction indicated that the synthesized compounds are non-toxic (LD50 350-

1000 mg/kg body weight). Consistent with the biological results, docking assays were performed to corroborate the antibacterial efficacy. These compounds showed potential as antibacterial agents and may function as foundational components for future, more efficacious medicines. The compounds may act as MurB inhibitors, as indicated by the docking prediction.



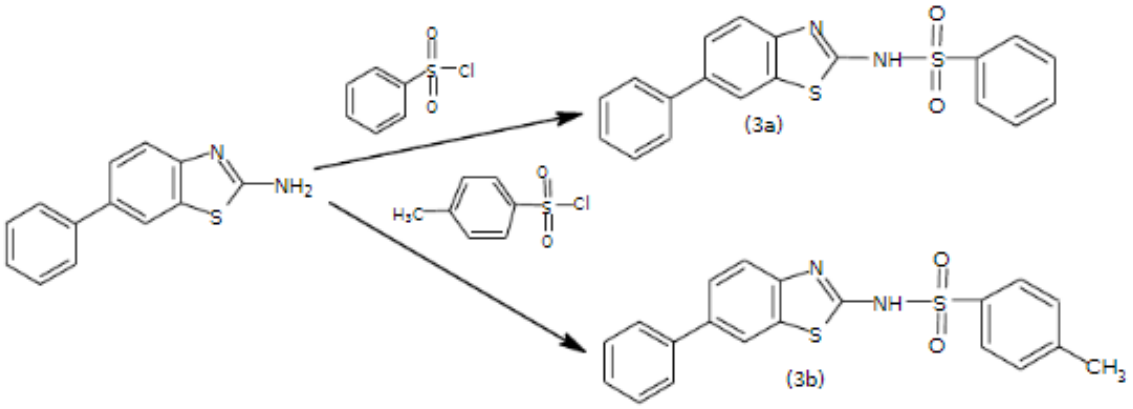
R: 1 =H, 2=4-OH, 3 =4-OCH_3, 4=4OH, 3-OCH_3, 5=2-Cl, 6=3-Cl, 7 =4-Cl, 8=2-NO_2, 9=3-NO_2, 10= 4-NO_2, 11=4OH, 3,5-OCH_3, 12 = 4-OH, 3-OCH_3, 5-I

The synthesis of diethyl 2-(2-benzothiazole-2-(3H)-ylidiene)-2-(cyano ethyl) malonate (8a) was detailed by **Fadda et al. (2019)**. The antimicrobial activity was evaluated after the determination of the structures of the novel compounds utilizing precise analytical and spectral data. Compounds exhibited the strong antibacterial activity against all tested strains.

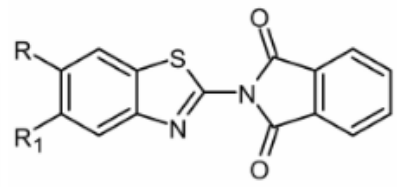
19a-c, 20, 22a,b

Onoja et al. (2020)aimed to synthesize hybrid compounds with improved antibacterial activities by the amalgamation of sulphonamide and benzothiazole. The N-(biphenyl-4-yl)thiourea used in the targeted sulphonamide synthesis was synthesized by a room-temperature reaction between diphenylamine and ammonium thiocyanate. Two sought-after sulphonamides, 3-amino-6-

phenylbenzothiazole and 3-para-toulene sulphonyl chloride, were synthesized, demonstrating antibacterial properties.



Carocci et al. (2023) proposed a unique family of benzothiazole-phthalimide hybrids. Two human breast cancer cell lines were used to assess the anticancer efficacy of these drugs. Researchers assessed the ability of compound 3h to induce damage to nuclear DNA. Furthermore, researchers used the broth microdilution method to examine the antibacterial efficacy, considering the established antimicrobial properties of the two scaffolds involved. Among all the chemicals examined, 3h had the most potent antibacterial activity against ESKAPE infections and Candida fungal strains.

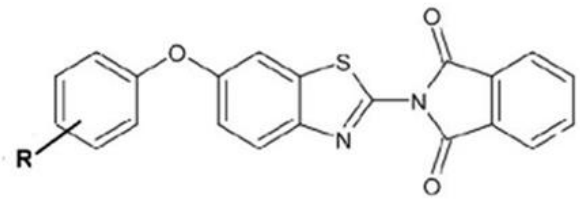


3a–h

a: R, R_1 = H
b: R = F, R_1 = H
c: R = CF_3, R_1 = H
d: R = CH_3, R_1 = H
e: R = OCH_3, R_1 = H
f: R, R_1 = OCH_3,
g: R = OH, R_1 = H
h; R = OPh, R_1 = H

To elucidate the mechanisms underlying the cyclodextrin (CD)-mediated enhancement of antimicrobial activity, **Carocci et al. (2025)** presented the synthesis and comprehensive characterization of a series of phenoxy-benzothiazole-phthalimide hybrid The proposed mechanism by which CDs decrease the least inhibitory concentration (MIC) values of antimicrobials is associated with their capacity to enhance the permeability of the bacterial cell

wall. This novel technique to exploit higher-order inclusion complexes may provide a potential approach to address microbial resistance.



Research Aims and Objectives: -

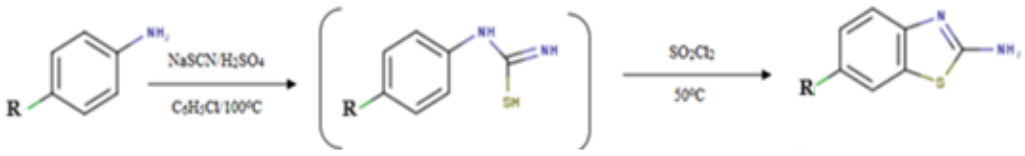
The current study has following objectives:

1. To synthesize novel benzothiazole derivatives.
2. To characterize the synthesized benzothiazole derivatives using advanced spectroscopic techniques such asNMR and IR spectrometry.
3. To evaluate the anti-diabetic activity of the synthesized derivatives.
4. To assess the anti-microbial potential of the synthesized derivatives.
5. To establish structure-activity relationships (SAR) for the synthesized derivatives by correlating chemical modifications with their observed biological activities.

Research Methodology & Materials: -

a) **Synthesis of benzothiazole derivatives:** Microwave-assisted synthesis will be employed to produce novel benzothiazole derivatives. MAOS (Microwave Assisted Organic Synthesis) is a contemporary method for the synthesis of organic compounds that is both safer and more environmentally friendly.Following procedure will be used for synthesis of substituted 2-aminobenzothiazoles:

   Scheme: The reaction of 4-substituted aniline and sodium thiocyanate under acidic condition to provide 2-amino-6-substituted benzothiazole.



The obtained BTA compounds will be further reacted to obtain novel derivatives.

b) **Characterization of synthesized compounds:** Elemental analysis, NMR spectra and IR spectra will be employed to characterize the synthesized compounds. The Perkin-Elmer model 2400 CHN elemental analyzers will be employed to conduct the elemental analysis. The Jeol ECX-500 spectrometer will be used to acquire HNMR spectra in DMSO-d6. The Nicolet 6700 FTIR spectrometer will be used to record IR spectra in KBr discs within the 4000-400 cm^{-1} range.

c) **Biological activity:** The anti-diabetic activity will be assessed using a specific form of the α-glucosidase enzyme inhibition assay. The synthesized compounds' anti-microbial activity will be assessed using different assays for anti-bacterial and anti-fungal activities.

Tentative Chapterization: -

Chapter 1 – Introduction

This chapter will provide an overview of benzothiazoles, emphasizing their importance in medicinal chemistry and their many biological functions. The chapter will delineate aims, scope and prospective implications for drug development, specifically for anti-diabetic and anti-microbial activities.

Chapter 2 - Review of Literature

A thorough examination of previous studies on benzothiazole derivatives will be provided. This chapter will examine prior research about their anti-diabetic and

anti-microbial characteristics and delineate the knowledge gaps that the research intends to fill.

Chapter 3 - Research Methodology/Materials and Methods

This chapter will delineate the comprehensive procedures for synthesizing new benzothiazole derivatives. The chapter encompasses the experimental methodologies, reaction parameters, and methods, including IR and NMR spectroscopy, used for structural characterisation.The methods used for biological assessment of the synthesized benzothiazole derivatives will also be discussed.

Chapter 4 – Result and Discussion

This chapter will discuss the results obtained during the research.

Chapter 5 – Conclusion and Future Scope

The fifth chapter will provide conclusion for the study based on the results of the study. It will also discuss the scope for future research.

Expected outcome of the proposed work: -

The proposed study is expected to result in the successful synthesis and structural characterization of novel benzothiazole derivatives with promising biological activities. Through comprehensive evaluations, the compounds are anticipated to exhibit significant antimicrobial and anti-diabetic activity. The findings may lead to the identification of potent lead compounds that can serve as candidates for further pharmaceutical development. Additionally, the research may contribute to the development of safer and more effective therapeutic agents, especially in the context of increasing microbial resistance and the global prevalence of diabetes.

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